

REMARKS

Claims 1-26, 33-40 and 61-74 are pending in the application. Claims 1-26, 33-36, 38-40, 61-69, and 71-73 are withdrawn from consideration. Claims 37 and 74 are currently amended to better clarify what applicants believe to be the invention. Support for the amendment can be found throughout the specification and in the claims as originally filed. No issue of new matter is believed to be introduced by this amendment. Applicants respectfully draw the Examiner's attention to the fact that claim 70, which was previously presented, is incorrectly listed as being withdrawn from consideration in the Office Action summary page, in line 4a), but within the text of the Office Action, has been rejected under 35 U.S.C. §112, first paragraph along with claims 37 and 74. Applicants respectfully request correction of this matter. Reconsideration of this application is respectfully requested.

Rejection under 35 U.S.C. §112

The Examiner has maintained his rejection of claims 37, 70 and 74 under 35 U.S.C. §112 for lack of enablement. The Examiner notes that while the specification is enabled for a method of screening an HIV-1 macrophage tropic (HIV M-tropic) fusion inhibitor with cells expressing both CD4 and CCR5 in the presence of M tropic HIV-1 infection or virus pseudotyped with a full-length of HIV M-tropic protein, wherein the inhibitor can be used for treating a patient infected with an M tropic HIV virus sensitive to said inhibitor, it does not reasonably provide enablement for a method of screening any or all HIV fusion inhibitors with a cell that only expresses CCR5 in the presence of any or all kinds of HIV isolates or any or all kinds of viruses pseudotyped with any or all kinds of M tropic envelopes, wherein an inhibitor identified by the method can be used for prevention of AIDS. More particularly, the Examiner has objected to the scope of the claim and has noted that the rejection would be overcome by deleting the recitation of "preventing".

Applicants respectfully traverse the Examiner's rejection and have amended claims 37 and 74 as suggested by the Examiner to delete the term "preventing" and as such, obviate the Examiner's rejection. Withdrawal of the rejection under 35 U.S.C. U.S.C. §112 is respectfully requested.

Rejection under 35 U.S.C. §102(a)

The Examiner has also maintained his rejection of claim 37 under 35 U.S.C. 102(a) as being anticipated by Cocchi, *et al.* (Science 1995, Vol. 270, pp. 1811-1815) in light of Moriuchi, *et al.* (J. Immunol. 1997, Vol. 159, pp. 5441-5449).

1. The Examiner's Position

The Examiner alleges that the claimed method for identifying an agent whether or not it can influence HIV-1, preferably M-tropic HIV-1 envelope fusion or entry into a target cell, comprises three elements, a) contacting an agent with a cell having a CCR5 expressed on the cell surface in the presence of an HIV virus or a virus pseudotyped with an HIV macrophage envelope b) measuring whether the agent can significantly inhibit the virus fused with the target cell or the cell developing resistance to virus fusion or entry and c) selecting the agent by measuring the cells resistance to fusion or entry of the macrophage tropic HIV in comparison to a group of another cell-virus system that does not contain the test agent.

The Examiner alleges that the method disclosed by Cocchi et al. contains all three elements: a) contacting the agent (recombinant C-C chemokine selected from the group consisting of recombinant human RANTES or MIP-1 α , or MIP-1 β or MCP-1) with the PM1 cell line in the presence of M-tropic HIV-1, such as HIV-1_{Bal} or T-tropic HIV-1 virus 2) They demonstrate the inhibitory effect of the test agent against both M-tropic and T-tropic HIV infection, and 3) they conclude that the M-tropic HIV-1 infection is inhibited by the chemokines.

2. Applicants' Response

Applicants respectfully traverse the rejection and have amended claim 37 to recite:

“A method for selecting for an agent for possible use in the treatment of an HIV infection caused by a macrophage-tropic HIV virus, wherein fusion of the macrophage-tropic virus to cells is mediated by CCR5...”.

As noted in the response to the previous Office Action, the patent law is settled that a rejection under 35 U.S.C. §102 is proper only if a single reference discloses every single element of an invention as claimed. The patent law is also clear that in certain circumstances a reference need not expressly disclose every single element of an invention as claimed if the element is inherent in the disclosure of the prior art. However, the patent law is equally clear that certain conditions must be met before an element may be found to be inherent in the disclosure of a prior art reference. The Examiner correctly outlines these conditions as settled by the Federal Circuit citing the review article of Feit et al. (2003, J. Pat. Trade Off. Soc., Vol. 85, No. 1, pages 5-21). The three conditions are as follows:

1. Certainty. The prior art reference must *necessarily* and *certainly* result in the invention as claimed including the elements of the claimed invention that are not expressly disclosed by the reference.
2. Chronology. The prior art reference must *always* result in the invention as claimed including the elements of the claimed invention that are not expressly disclosed by the reference.
3. Recognition. One of ordinary skill must *recognize* that the elements of the claimed invention that are not expressly disclosed by the reference are present in the disclosure of the prior art reference.

Cocchi et al. do not meet a single of these three criteria as required by the law

Applicants respectfully point out to the Examiner that Cocchi et al. do not teach or suggest all of the limitations of claim 37 as currently amended, either expressly or inherently. The Examiner acknowledges that *Cocchi et al. do not teach or suggest* a method of selecting an agent for possible use in the treatment of an HIV infection caused by a macrophage-tropic HIV virus, *wherein entry of the macrophage-tropic virus into cells is mediated by CCR5*, the method comprising contacting the agent with a cell in the presence of the macrophage tropic virus and monitoring whether the virus fuses with the

cell in the absence of the agent but does not fuse with the cell in the presence of the agent. Moreover, the claim has been amended to recite “fusion” rather than “entry”. Therefore, not a single one of the foregoing requirements for a rejection based upon inherency are met regarding this element of the claimed invention. *Cocchi et al. do not teach or suggest that chemokines such as RANTES, MIP-1 alpha or MIP-1 beta prevent the virus from fusing with the cell surface*, as recited in the currently amended claims. As noted in the reply to the previous Office Action, and reiterated here, *the role of CCR5 as a co-factor for viral fusion with the cell was not known at the time the Cocchi et al. reference was published*. Cocchi et al. clearly believed that the chemokines exerted their effect *subsequent* to viral fusion to the cell. Moreover, as noted in the response to the previous Office Action, Cocchi et al. specifically state on page 1814 in the middle column, second paragraph:

“Chemokine-mediated control of HIV may occur either directly, through their inherent anti-lentiretroviral activity, or indirectly, through their ability to chemoattract T cells and monocytes in proximity of the infection loci.”

Cocchi et al. **do not teach or suggest** the fact that the chemokines **prevent fusion of the virus to the cell membrane**, as currently claimed. The fact that Cocchi et al. teach inhibition of viral replication is not equivalent to the teachings of the present invention. Applicants assert that there are many other means by which a compound/chemokine may prevent viral replication, including events that are post fusion and post entry of the virus into the cell. In fact, Cocchi et al. **do not teach or suggest** the methods of inhibition of viral fusion with the cell membrane using the chemokines. It was only at the time of the present invention that such knowledge became available. Therefore, not a single one of the foregoing three requirements for a rejection based upon inherency are met regarding this element of the claimed invention.

Furthermore, as also noted previously, at the time the Cocchi et al. reference was published, *the CCR5 receptor had not yet been identified, nor had its role as a co-factor with CD4 for viral fusion with cells been elucidated*. Therefore, given the lack of knowledge at the time of publication of the Cocchi et al. reference of the very existence

of the CCR5 receptor, it certainly cannot be that one of skill in the art would recognize that this element of the invention as claimed was present in the teachings of Cocchi et al. Moreover, based upon the teachings of Cocchi et al. **there would have been no motivation to screen for agents that block fusion of the HIV macrophage-tropic strains of virus to cells expressing both CD4 and CCR5, as presently claimed.** Cocchi et al. clearly do not teach or suggest that the chemokines block viral fusion with the cell membrane. It is Applicants' position that Cocchi et al. teach that inhibition of viral replication by the chemokines occurs subsequent to viral fusion, and as such, they do not teach the methods of the present invention, as currently claimed, that is, that the chemokines act to prevent viral "fusion" to the cell membrane.

3. The Examiner's non-specific rejection based upon a combination of references

The Examiner also alleges that the claims of the present application are inherent based on the teachings of Cocchi et al. in view of Moriuchi et al. Applicants believe that the Examiner intends to reject the pending claims as unpatentable under 35 U.S.C. §103 though no such rejection is made. Applicants note that a rejection under 35 U.S.C. §103 may also rely upon inherent disclosure of elements of the invention as claimed that are not expressly taught by the prior art references. The law of inherency is the same as applied to a rejection under 35 U.S.C. §103 as it is when applied to a rejection under 35 U.S.C. §102.

4. Applicants' Response to the non-specific rejection based upon a combination of references

(a) *The Examiner fails to set forth a proper *prima facie* case of obviousness*

Applicants remind the Examiner that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further remind the Examiner that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed (the law of inherency may be applied for those elements not expressly disclosed

by the references in combination); 2) there must be some suggestion or motivation in the prior art to combine the references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in the making the combination to reach the invention as claimed.

Any alleged combination of references in the present situation fails the most basic test for the appropriateness of a rejection. **The Examiner previously admitted that Cocchi et al. do not teach or suggest the presence of a CCR5 receptor, and the Examiner also previously admitted that Moriuchi et al. is not prior art. The references simply cannot be combined.**

(b) The Examiner confuses the relevant time of inquiry

The Examiner apparently offers Moriuchi et al. for the teaching of a CCR5 receptor. The Examiner is reminded that the patent law clearly states that

A patent may not be obtained...if the difference between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious *at the time the invention was made*... 35 U.S.C. §103.

Moriuchi et al published their findings after Applicants' earliest priority date. As such, Moriuchi et al. may not be used as a secondary reference for a rejection under 35 U.S.C. §103. Likewise, Moriuchi et al. may not be used as evidence of what was known in the art at the time Applicants' both made their invention and filed the instant patent application.

(c) The Examiner offers contradictory statements

The Examiner previously summarized the three criteria for inherency, the most important one being certainty, and **certainty is established when the reference necessarily results in the claimed process as opposed to a possibility**. Applicants respectfully point out to the Examiner that such certainty can be questioned if one takes into account the Examiner's own comments regarding unpredictability as well as the reference cited on page 6, paragraph 19 of the previous Office Action (Igarashi et al. J. Virol. 2003, Vol. 13042-13052). In particular, as the Examiner notes:

“...not all M-tropic envelope mediated fusion uses CCR5.....Therefore, it is unpredictable for using a virus pseudotyped with any or all kinds of macrophage-tropic envelope protein to do the R5 mediated fusion inhibitor screening assay.”

Furthermore, with respect to the second criterion, that is, it will always happen, Applicants assert that once again, as the Examiner has previously pointed out, in some cases, it may not happen. That is, as the Examiner has noted in the previous Office Action on page 6, paragraph 19 :

“...not all M-tropic envelope mediated fusion uses CCR5.”

(d) The Examiner's colleagues have already settled the issues being discussed herein

Applicants respectfully direct the Examiner's attention to the file history for Applicants' previously issued patent, U.S. Patent 6,258,527, issued on July 10, 2001 from which the present application is a continuation application. Moreover, Applicants previously disclaimed the patent term of the present application, which might extend beyond that of the subject patent U.S. 6,258,527 and enjoying a presumption of validity. The Examiner's colleague, Robert Budens from art unit 1648, expressly states in the file history in an Office Action dated August 31, 1999, on page 5 of Paper No. 14, that:

“The claimed invention appears free of the art. The art does not disclose or fairly suggest cell lines as set forth in claim 41 or methods of using such cell lines for identifying inhibitors of HIV infection.”

Based on the foregoing, withdrawal of the rejection is respectfully requested.

Fees

A check in the amount of \$60. to cover the petition for a one month extension of time is enclosed. No other fees are believed to be necessitated by the foregoing Response. However, should this be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusions

Applicants believe that the foregoing arguments and amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,



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